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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/597,305	07/19/2006	Inpyo Choi	58049-00034	9091

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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
06/03/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

uspto@jhkiplaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/597,305	CHOI ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2010 and 13 May 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 May 2010* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This supplemental action is being mailed to address the papers filed 5/13/2010, which crossed in the mail with the Office action mailed 5/13/2010.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/4/2010 has been entered.

Receipt is acknowledged of an amendment, filed 5/4/2010, in which claims 37 and 39 were canceled, and claims 29 and 38 were amended. Claims 29 and 38 are pending.

Election/Restrictions

Applicant elected Group II and ferritin H chain (BC 012314) gene with traverse in the reply filed on 1/19/2009.

Claims 29 and 38 are under consideration.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). Receipt of the certified copy of the foreign priority document, KOREA 10-2004-0004308, is acknowledged. These papers have been placed of record in the file.

Specification

The amendment filed 7/28/2009 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the amino acid sequence of SEQ ID NO: 49.

At page 12 of the reply filed 7/28/2009, the response asserts that Ferritin H chain (BC12314) is described in the specification as originally filed. Further, the response asserts that an ordinary person in the art can easily search protein sequence and nucleotide sequence from BC12314 by using the NCBI website. The response notes that this is the first time the sequence is presented, but it should not be considered to be new matter because the sequence was available to the public and the specification as originally filed stated where the sequence information could have been found.

The specification as originally filed fails to provide literal or inherent support for the sequence of SEQ ID NO: 49. The original claims present on the filing date are accepted as a clear intent to incorporate the nucleic acid sequence of GenBank Accession No. BC12314. The originally filed claims were drawn to treating cells with an effective amount of a ferritin H chain (BC012314) gene. GenBank Accession No. BC012314 (GI: 15126787, publicly available August 2001) describes a cDNA clone of the *Mus musculus*, ferritin heavy chain gene. The entry is directed to the nucleic acid sequence, and the originally filed claims were directed to the administration of a gene (i.e., nucleic acid). The originally filed application did not convey

intent to incorporate the amino acid sequence described as the coding sequence of ferritin heavy chain with the GenBank Accession No. BC12314 features description.

Applicant is required to cancel the new matter in the reply to this Office Action.

Response to Arguments – Specification

Applicant's arguments filed 5/4/2010 have been fully considered but they are not persuasive. At page 4, the response traverses the Examiner's position that the amendment filed 7/28/2009 introduced new matter into the disclosure. The response does not provide specific reasons in the traversal. Therefore, the arguments are not found persuasive. The new matter has not been canceled from the disclosure. Therefore, the objection is maintained.

Response to Arguments - Double Patenting (Warning)

The provisional objection of claim 39 is moot in view of Applicant's cancellation of claims 37 and 39 in the reply filed 5/4/2010.

Response to Arguments - Claim Objections

The objection of claim 36 is moot in view of Applicant's cancellation of the claim in the reply filed 5/4/2010.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29 and 38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

In the reply filed 5/4/2010, claim 29 was amended to require the step of "treating the hematopoietic stem cells with an effective amount of ferritin H chain (BC012314) and IL-15 *in vitro*." Claim 38 was amended to require the step of "treating the premature natural killer cells, with an effective amount of ferritin H chain (BC012314) and IL-15 *in vitro*."

The first version of claim 29 was directed to the step of treating premature natural killer cells with an effective amount of ferritin H chain (BC012314) gene. Furthermore, the recitation of GenBank Accession No. BC012314 in the originally filed claims, in the context of ferritin H chain gene as a differentiation agent, is interpreted as intent to incorporate the nucleotide sequence of BC012314. GenBank Accession No. BC012314 (GI: 15126787, publicly available August 2001) is a nucleotide sequence record that describes a cDNA clone of the *Mus musculus*, ferritin heavy chain gene. The originally filed disclosure is directed only to the administration of ferritin H chain gene to cells (e.g., page 1, lines 8-12; page 3, lines 18-22; page 4, lines 21-24; pages 7-9; paragraph bridging pages 11-12). The originally filed disclosure does not provide support for the treatment of cells with a protein encoded by the nucleotide sequence of BC012314. As written, claim 29 does not limit the administration of "ferritin H chain

(BC012314)" to the administration of a nucleic acid sequence. Given the broadest reasonable interpretation, the claims read on the administration of protein or nucleic acid.

The specification provides support for the culture of hematopoietic stem cells (HSCs) for six days to differentiate the cells to pNK cells, followed by the culture of the cells with OP9 stromal cells and IL-15 protein (e.g., page 24, lines 11-24; page 25, lines 1-13). Culture of the pNK cells in the presence of OP9 stromal cells and IL-15 protein resulted in the differentiation of the pNK cells to mNK cells (e.g., paragraph bridging pages 25-26). The originally filed disclosure does not provide support for the treatment of cells with a protein encoded by the nucleotide sequence of BC012314. Support for the administration of IL-15 nucleic acid (e.g., GenBank U14332) could not be found. The specification teaches that IL-15 nucleic acid was only detected n HSC and pNK cells (e.g., page 32). Support could not be found for the treatment of the cells with a combination of ferritin H chain (BC012314) and IL-15.

The original specification, drawings and claims were thoroughly reviewed and no support could be found for the amendment. Accordingly, the amendment is a departure from the specification and claims as originally filed, and the recitation of ferritin H chain (BC012314) gene in the originally filed claims and specification does not provide support for the full scope of the claims as amended.

Claims 29 and 38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection was made in

the Office action mailed 11/5/2009 but has been rewritten to address the amendments to the claims in the reply filed 5/4/2010.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: Claim 29 is drawn to a method of differentiating a hematopoietic stem cell (HSC) into a mature natural killer (mNK) cell, comprising treating the HSCs with an effective amount of ferritin H chain (BC012314) and IL-15 *in vitro*. Claim 38 is drawn to a method of differentiating a premature natural killer (pNK) cell to a mNK cell, comprising treating the pNK cells with an affective amount of ferritin H chain (BC012314) and IL-15 *in vitro*. The nature of the invention is complex in that the combination of ferritin H chain (BC012314) and IL-15 must be sufficient to differentiate HSCs or pNK cells to mNK cells.

Furthermore, claims 29 and 38 encompass the administration of the ferritin H gene claimed as GenBank accession number BC012314. Thus, the nucleic acid sequence of BC012314 is essential to the practice of the claimed invention. The specification discloses that the "mark in the bracket after the name of gene means GenBank ID implying sequence of each gene and the GenBank ID can be easily searched and used by the people in this field" (page 5, lines 11-14). Essential material may be incorporated by reference, but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference.

The original claims present on the filing date are accepted as clear intent to incorporate the sequence by reference; however, essential material cannot be incorporated from the GenBank database. The sequence of BC012314 is required to enable the method of administering the gene sequence. This sequence is present in the specification as SEQ ID NO: 50.

Breadth of the claims: The claims do not specifically limit the ferritin H chain (BC012314) and IL-15 to nucleic acid or protein. The originally filed specification provides support for the separate administration of ferritin H chain gene and IL-15 protein. The recitation of ferritin H chain (BC012314) and IL-15 does not explicitly limit the compound administered to either a nucleic acid or protein.

Guidance of the specification: The specification asserts that ferritin H gene (BC012314) is a differentiation regulating agent for natural killer cells (e.g., page 6). The specification asserts that the gene can be used to regulate the differentiation of pNK cells to mNK cells and to treat cancers (e.g., page 10, line 21 to page 12, line 23). The specification provides general guidance with regard to the administration of pharmaceutical formulations and envisions the use of oral or parenteral administration of the gene (e.g., page 12, line 25 to page 14, line 8).

The specification teaches the isolation of hematopoietic stem cells (HSCs) from the tibia and femur of a C57BL/6 mouse (e.g., paragraph bridging pages 22-23). The cells had over 96% purity (e.g., page 23, lines 9-13). The specification teaches that the mouse HSCs can be differentiated *in vitro* to pNK cells and further differentiated *in vitro* to mNK cells (e.g., page 23, line 15 to page 24, line 24). To differentiate the HSCs to pNK cells, the HSCs were cultured in RPMI complete medium supplemented with mouse SCF, mouse Flt3L, mouse IL-7, indomethacin, gentamycin and 10% fetal bovine serum (e.g., paragraph bridging pages 23-24).

After 6 days in culture, the cells had differentiated to form pNK cells, which are CD122+ cells. The cells had over 92% purity (e.g., paragraph bridging pages 23-24). To induce the differentiation of pNK cells to mNK cells, the CD122+ cells were incubated with OP9 stromal cells in the presence of mouse IL-15 protein. On day 12, NK1.1+ cells were obtained (e.g., page 24, lines 11-24). The specification teaches the analysis of gene expression from HSCs, pNK and mNK cells using Serial Analysis of Gene Expression (SAGE) (e.g., page 26, line 9 to page 39, line 1). The specification discloses 30 different genes that were identified by the SAGE procedure as specifically expressed at the pNK cell stage. These genes are recited in Table 4 at pages 35-37 of the specification. Ferritin H chain (BC012314) is included in this table at row 2. Further, the expression of Ferritin H chain was studied by RT-PCR using the primers disclosed as SEQ ID NOs: 27 and 28 (e.g., page 39, line 1 to page 41, line 18). By RT-PCR analysis ferritin H chain (BC012314) expression was detected in HSC, pNK, mNK (-OP9) and mNK (+OP9) (Figure 4B). The specification teaches that IL-15 nucleic acid was only detected n HSC and pNK cells (e.g., page 32), unlike ferritin H chain (BC012314).

Existence of working examples: No working examples of the claimed method are provided. No working examples are provided that demonstrate the ability of ferritin H chain protein or gene to induce HSC or pNK cell differentiation to form mNK cells in the presence of only IL-15. Differentiation is shown of HSC to pNK cells under culture conditions lacking ferritin H chain and lacking IL-15. Differentiation of pNK cells to mNK cells in the presence of IL-15 protein and OP9 stromal cells is shown. However, differentiation of pNK cells to mNK cells absence of OP9 stromal cells is not shown for ferritin H chain gene or protein.

Predictability and State of the art: The state of the art with regard to involvement of

ferritin H gene in controlling the differentiation of pNK cells to mNK cells was underdeveloped at the time the invention was made. The prior art teaches that ferritin is a ubiquitous and highly conserved iron-binding protein composed of two subunits termed H and L (Torti et al. The Journal of Biological Chemistry, Vol. 263, No. 25, pages 12638-12644, 1988, cited in a prior action; e.g., page 12638, right column, 3rd full paragraph). Torti et al teach that ferritin functions in the storage and delivery of iron for intracellular use, and it functions in detoxification of elemental iron, which is toxic in a non-complexed form (e.g., page 12638, right column, 3rd full paragraph). Thus the prior art does not provide clear support for a role for ferritin H chain (BC012314) in natural killer cell differentiation, and the specification does not provide evidence that increased expression of ferritin H chain (BC012314) by delivering a protein or nucleic acid molecule comprising the sequence of BC012314 to HSCs or pNK cells in combination with IL-15 will be sufficient to induce differentiation to mNK cells. Accordingly, the effects of exogenous BC012314 expression on natural killer cell differentiation would have been unpredictable.

Amount of experimentation necessary: The quantity of experimentation necessary to carry out the claimed invention is high, as the skilled artisan could not rely on the prior art or the present specification to teach how to use the claimed methods. One would be required to perform a large amount of trial and error experimentation to use the ferritin H chain and IL-15 genes and/or proteins to induce the differentiation of HSCs or pNK cells to mNK cells. The prior art does not teach a role for ferritin H chain in the differentiation of NK cells, the specification does not provide evidence that ferritin H chain in combination with IL-15 is sufficient to induce NK cell differentiation, and the specification teaches detectable expression of

ferritin H chain in HSCs, pNK cells, and mNK cells by RT-PCR. Thus, ferritin H chain expression would already be present in the differentiating cells. It would require a large quantity of trial and error experimentation by the skilled artisan to carry out the claimed invention.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 29 and 38 are not considered to be enabled by the instant specification.

Response to Amendment – Declaration of Dr. Inpyo Choi

The declaration under 37 CFR 1.132 filed 7/28/2009 is insufficient to overcome the rejection of claims 29 and 38 based upon insufficiency of disclosure under 35 U.S.C. 112, first paragraph, as set forth above. **The declaration has not been signed**. Even if the declaration were signed, it would not be sufficient, because the evidence presented is not commensurate in scope with the claims.

The claimed invention requires the administration of a ferritin H chain (BC012314) and IL-15. The claims do not limit these molecules to proteins. Further, claim 29 requires ferritin H chain (BC012314) and IL-15 to be capable of differentiating hematopoietic stem cells (HSCs) into mature natural killer (mNK) cells.

At paragraph 6, the declaration states that to confirm whether pNK-specific expression of Ferritin H was required for the differentiation into mNK, hematopoietic stem cells (HSCs) were cultured for 6 days, and then treated with IL-5 and Ferritin H in the absence of OP9 stromal cells, followed by measuring the percentage of NK cells. At paragraph 7, it is stated that HSCs were

treated with IL-15 and Ferritin H together, or IL-15 only (presumably reference to IL-5 in paragraph 6 is a typographical error). At paragraph 7, it is disclosed that the use of IL-15 and Ferritin H together, increased the percentage of NK cells as compared to treatment with IL-15 alone. The results also appear to be presented in a figure attached as Exhibit B; however, this exhibit is not specifically referred to in the declaration.

The evidence is not commensurate in scope with the claimed invention. The declaration does not demonstrate that Ferritin H chain alone is sufficient to induce NK cell differentiation from HSCs to a mNK cell. The present specification teaches that the 6 days of culture of the HSCs results in differentiation of the cells to premature NK (pNK) cells (e.g., page 25, lines 3-7). The evidence presented demonstrates that the combination of IL-15 protein and ferritin H chain protein is better than IL-15 protein alone to induce differentiation of mNK cells from pNK cells. Claim 29 requires the differentiation of HSCs to mNK cells, rather than pNK cells to mNK cells. Further, the claims read on the administration of protein or nucleic acid.

The evidence presented is not sufficient to overcome the *prima facie* case of non-enablement.

Response to Arguments - 35 USC § 112

The rejection of claims 37 and 39 under 35 U.S.C. 112, second paragraph, is moot in view of Applicant's cancellation of the claims in the reply filed 5/4/2010.

The rejection of claims 37 and 39 under 35 U.S.C. 112, first paragraph (new matter) is moot in view of Applicant's cancellation of the claims in the reply filed 5/4/2010.

With respect to the rejection of claims 29 and 38 under 35 U.S.C. 112, first paragraph (new matter), Applicant's arguments filed 5/4/2010 have been fully considered but they are not persuasive.

The response traverses the rejection but does not provide any specific reasons as to why the rejection should be withdrawn, except that claim 29 does not recite "SEQ ID NO: 49." However, the amended claims are now drawn to the administration of ferritin H chain (BC012314) and IL-15. The claims do not limit the ferritin H chain (BC012314) and IL-15 to nucleic acid or protein. The originally filed specification provides support for the separate administration of ferritin H chain nucleic acid (gene) and the administration of IL-15 protein to pNK cells. The originally filed specification does not provide support for the administration of ferritin H chain protein, IL-15 gene, or the combined administration of ferritin H chain and IL-15 to HSC or pNK.

For these reasons and the reasons made of record above, the rejection is maintained.

The rejection of claims 37 and 39 under 35 U.S.C. 112, first paragraph (enablement) is moot in view of Applicant's cancellation of the claims in the reply filed 5/4/2010.

With respect to the rejection of claims 29 and 38 under 35 U.S.C. 112, first paragraph (enablement), Applicant's arguments filed 5/4/2010 have been fully considered but they are not persuasive.

The response asserts that the Examiner has indicated that Dr. Choi's Declaration shows that the combination of IL-15 protein and ferritin H chain protein works better than IL15 protein alone to induce differentiation of MK cells from HSCs. The response asserts that the claims recite this feature. Thus, the response asserts that the rejection has been overcome.

These arguments are not found persuasive. The Declaration of Dr. Choi cannot be relied upon to overcome the rejection of record, because it is not signed. Furthermore, a review of the declaration indicates that the experiments are only directed to the differentiation of pNK to mNK in the presence of ferritin H chain protein and IL-15 protein. For the reasons discussed above with regard to the Declaration of Dr. Choi, these results are not commensurate in scope with the claims.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is (571)272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR

system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer Dunston/
Primary Examiner
Art Unit 1636